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Transmitted herewith for filing is the patent application of

Inventor(s): **P. Törmälä; M. Kellomäki; W. Bonfield; K. Tanner**For : **BIOACTIVE AND BIODEGRADABLE COMPOSITES OF POLYMERS AND CERAMICS OR
GLASSES AND METHOD TO MANUFACTURE SUCH COMPOSITES**

Enclosed are:

1. **16** sheets of specification, **1** sheet of claims, and **1** sheet of abstract.
2. **2** sheet(s) of drawings.
3. Unsigned Declaration and Power of Attorney.

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BASIC FEE			770.00	\$770.00
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Dated:

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BIOACTIVE AND BIODEGRADABLE COMPOSITES OF POLYMERS AND CERAMICS OR GLASSES AND METHOD TO MANUFACTURE SUCH COMPOSITES

Field of the Invention

The present invention relates to a surgical osteosynthesis composite material, which is biodegradable and bioactive, and methods of manufacturing the composite material.

5

Background of the Invention

In surgery, either biostable or biodegradable devices are used for the fixation of bone fractures to immobilize the bone fragments and accelerate patient mobilization.

10 Most biostable devices are typically made of metallic alloys. *See* R.M. Pilliar, Powder Metal-Made Orthopaedic Implants With Porous Surface For Fixation By Tissue Ingrowth, *Clinical Orthopaedics and Related Research*, Vol. 176, 1983, pp. 42-51. Nevertheless, there are several disadvantages in the use of metallic implants. One such disadvantage is bone resorption caused by bone plates and screws, which
15 carry most of the external loads, leading to stress protection produced by the

modulus mismatch between metals and bone. Another disadvantage is the carcinogenic potential and the possibility of corrosion. Therefore, surgeons are recommended to remove metallic bone plates and screws in a second operation once the fracture has healed.

- 5 Bioresorbable polymeric fracture fixation devices have been studied as replacements for metallic implants. *See* S. Vainiopää, P. Rokkanen, P. Törmälä, Surgical Applications Of Biodegradable Polymers In Human Tissue, Progress in Polymer Science, Vol. 14, 1989, pp. 679-716. The advantages of these devices are that materials resorb in the body and degradation products disappear via metabolic
- 10 routes. Hence, a second operation is not required. Additionally, the strength and the stiffness of the bioresorbable polymeric devices decreases when the device degrades and hence the bone is progressively loaded (which promotes bone regeneration). One disadvantage is the relatively low strength of existing polymeric devices. In the case of cortical, bone fracture, for example, unreinforced poly lactic acid (PLLA)
- 15 plate and screws are too weak initially to permit patient mobilization. *See* J. Eitenmüller, K.L. Gerlach, T. Schmickal, H. Krause, An In Vivo Evaluation Of A New High Molecular Weight Polylactide Osteosynthesis Device, European Congress on Biomaterials, Bologna Italy, September 14-17, 1986, p. 94. In addition, the relatively low values of Young's modulus compared to metallic plates mean that
- 20 thicker sections are required to ensure adequate stability.

Törmälä et al. have developed self-reinforced bioresorbable polymeric composites to improve the strength of bioresorbable polymer devices. These show good mechanical properties: e.g. bending strengths of 360 ± 70 MPa and bending moduli of 12 ± 2 GPa, respectively, have been reported. *See* P. Törmälä,

Biodegradable Self-Reinforced Composite Materials; Manufacturing, Structure and Mechanical Properties, Clinical Materials, Vol. 10, 1992, pp. 29-34.

A common property of most polymeric implants is the lack of bony ongrowth to the material. In contrast, such bone apposition is produced by bioactive ceramics and glasses. See O.H. Andersson, K.H. Karlsson, Bioactive Glass, Biomaterials Today And Tomorrow, Proceedings of the Finnish Dental Society Days of Research, Tampere, Finland, 10-11 November 1995, Gillot Oy, Turku, 1996, pp. 15-16. By adding bioactive ceramics or glasses to polymers to produce a composite, the bioactivity of the material can be improved. This effect has been demonstrated in dental composites and bone cement. See J.C. Behiri, M. Braden, S.N. Khorashani, D. Wiwattanadate, W. Bonfield, Advanced Bone Cement For Long Term Orthopaedic Applications, Bioceramics, Vol. 4, ed. W. Bonfield, G.W. Hastings and K.E. Tanner, Butterworth-Heinemann ltd, Oxford, 1991, pp. 301-307.

Bonfield et al have developed a biostable composite consisting of a polyethylene matrix and a particulate hydroxyapatite reinforcement (HAPEX™). See W. Bonfield, J.A. Bowman, M.D. Gryn timer, UK Patent GB2085461, 1984. HAPEX™ composites show bioactivity above 0.20 volume fraction hydroxyapatite. See W. Bonfield, C. Doyle, K.E. Tanner, In Vivo Evaluation Of Hydroxyapatite Reinforced Polyethylene Composites, Biological and Biomechanical Properties of Biomaterials, ed., P. Crystel, A. Meunter, A.J.C. Lee, Elsevier Science Publisher, 1986, pp. 153-158. Additionally, degradable composites of hydroxyapatite and copolymers of polyhydroxybutyrate and polyhydroxyvalerate have been described. See C. Doyle, K.E. Tanner, W. Bonfield, In Vitro And In Vivo Evaluation Of Polyhydroxybutyrate And Of Polyhydroxyvalerate Reinforced With Hydroxyapatite,

Biomaterials, Vol. 12, 1991, pp. 841-847. The main limitation of these biostable and biodegradable composites is their inadequate mechanical strength for large bone fracture fixation. Also, use of hydroxyapatite and poly lactic acid composites has been reported. See Y. Ikada, H.H. Suong, Y. Shimizu, S. Watanabe, T. Nakamura,

5 M. Suzuki, A.T. Shimamoto, Osteosynthetic Pin, U.S. Patent 4,898,186, 1990.

Using existing elements the composite still has quite moderate mechanical strength.

Also in all these cases mentioned above the method of producing the composite differs from the method of the present invention.

10 Summary of the Invention

In this invention, we have established that the problems of inadequate strength and the brittleness of the bioactive bone fixation devices and the lack of bioactivity of absorbable polymeric devices are resolved by constructing a composite material comprising at least one resorbable polymeric matrix, at least one bioactive ceramic
15 reinforcing element and at least one resorbable polymeric reinforcing component.

The composite material described in more detail herein consists of two reinforcing components in a matrix material. One reinforcing element, the polymeric reinforcing element, is comprised of biodegradable polymer fiber and the other, called the ceramic reinforcing element, is comprised of bioceramic or bioglass.

20 Reinforced composite devices described in this invention have improved mechanical properties compared to non-reinforced devices, because reinforcement changes the behavior of material from brittle to ductile and thus makes device more reliable under load. Due to controlled manufacturing stages, mixing of matrix and ceramic reinforcing element as well as combining the polymeric reinforcing element, the

amount of both reinforcing element types is easily controlled. This is an important advantage, because the ratio of elements affects the mechanical properties of the device. Also, the amount of the ceramic reinforcing element affects the bioactivity of the device.

5

Brief Description of the Drawings

Figure 1 Shows a schematic picture of the cross-section of a composite plate of the invention.

Figure 2a Shows a FTIR spectrum of hydroxyapatite,

10 Figure 2b Shows a FTIR spectrum of hydroxyapatite-poly lactic acid composite, and

Figure 2c Shows a FTIR spectrum of poly lactic acid composite.

Description of the Preferred Embodiments

15 This invention relates to biodegradable materials used for bone fracture fixation devices and methods of their manufacture. Unlike other known materials used prior to this application, the composites of this invention have two different reinforcing phases and one matrix phase. One reinforcing element is referred as the polymeric reinforcing element and the other as the ceramic reinforcing element. The
20 matrix component can be any biodegradable or bioerodible polymer. Typical examples of these polymers are listed in Table 1 herein.

One reinforcing phase is a totally or at least partially oriented and/or fibrillated biodegradable or bioerodible polymer. This phase is called the polymeric reinforcing element, which is still recognizable and distinguishable from the final

product as a whole. The diameter of the reinforcing fibers can vary between 4 μm and 800 μm , preferably between 20 μm and 500 μm . Useful polymers for the polymeric reinforcing element include those listed in Table 1.

The ceramic reinforcing element can be comprised of a stable or a degradable bioceramic or bioglass, or a mixture of these. Typical examples are listed in Table 2. They can be used in a powder, flake, spherical, fiber or any other form. Particle size can vary between 2 μm and 100 μm , preferably between 60 μm and 150 μm . In the case of fibers, the fibers are in all cases smaller than the polymeric reinforcing elements. The ceramic reinforcing element also acts as a bioactive, bony ongrowth agent and provides a reservoir of calcium and phosphate ions, thus accelerating the healing time for bone fractures. While the matrix polymer degrades, bone can attach to the residual ceramic or glass particles. The amount of ceramic reinforcing element is 0.15 to 0.9 volume fraction, preferably between 0.2 and 0.6 volume fraction.

The defined particle size of the ceramic element in the composite described in this invention is relatively big compared to conventionally used particle sizes for fillers or granules. In this invention, it was found unexpectedly that composites having bigger particle size ceramic elements are more biocompatible and cause less irritation to tissue than composites utilizing a ceramic element having small particle size. Biocompatibility is easily seen in histological studies. In tissue near and inside the degrading composite implants having small ceramic particles there exists more giant cells than around and inside the degrading composite implants containing big (coarser) ceramic particles.

The invention may contain various additives and modifiers which improve the processability of the composite. Such additives include surface modifiers to improve

the attachment between the polymeric and ceramic components. The devices can also contain pharmaceutically active agent or agents, such as antibiotics, chemotherapeutic agents, wound-healing agents, growth hormones and anticoagulants (such as heparin). These agents are used to enhance the bioactive
5 feature of the composite and thus improve the healing process of the tissue.

Manufacture of the composite can be performed by any suitable plastics technology processing method. The matrix polymer and the ceramic reinforcing element(s) (bioceramic or bioglass) can be mixed together by powder mixing, melt mixing or solvent mixing. The polymeric reinforcing element (polymer fiber) can be
10 used as plain fiber or in modified form: for example, as braided or woven two or three dimensional structures. The mixture of matrix and the ceramic reinforcing element can be combined with the polymeric reinforcing element by melt mixing, by coating or by using solvent as an intermediate to preform the material (prepreg). The material can be produced in its final form by various techniques, including
15 compression molding, filament winding, mechanical machining or injection molding to any desired shape.

Due to controlled manufacturing stages, mixing of matrix and ceramic reinforcing element as well as combining the polymeric reinforcing element, the amount of both reinforcing element types is easily controlled. This is an important
20 advantage, because the ratio of elements affects the mechanical properties of the device. Also, the amount of the ceramic reinforcing element affects the bioactivity of the device. There should be sufficient bioceramic or bioglass to yield bony ongrowth.

Reinforced composite devices described in this invention have improved mechanical properties compared to non-reinforced devices, because reinforcement

changes the behavior of the material from brittle to ductile and thus makes the reinforced device more reliable under load. This feature is very important for load bearing applications, such as bone fracture fixation devices. For example, non-reinforced poly lactic acid devices typically have three-point bending strengths of 35-40 MPa and moduli of 3.5-4.0 GPa, and particulate reinforced (hydroxyapatite) poly lactic acid devices have values of 25-30 MPa and 5.0 GPa, respectively. Using polymer fiber reinforcement under the present invention, mechanical properties of two to five times higher are achieved.

10 EXAMPLES

The present invention is described in more detail by means of the following, non-limiting examples.

Example 1.

15 Plates sized approximately 50 x 10 x 2 mm were manufactured by compression molding from a powder mixture of poly (L,D-lactide) (95/5 L/D ratio) and hydroxyapatite with particle size of 60 μ m, reinforced unidirectionally with poly (L-lactide) fibers (53/35/12 weight percent of matrix polymer-hydroxyapatite - polymer fiber, respectively). Three-point bending strength (yield) and modulus were 20 69.8 MPa and 5.8 GPa, respectively, and no sample fracture was detected (ductile behavior). These results were compared to the results of similarly sized samples without fiber reinforcement, compression molded from (1) plain PLDLA 95/5 and from (2) powder mixture of PLDLA 95/5 and hydroxyapatite (60/40 w/w %). These samples showed three-point bending strengths (maximum) and moduli of (1): 38.0

MPa and 3.9 GPa and (2): 26.8 MPa and 5.0 GPa, respectively. These samples broke in bending without yielding, thus showing brittle fracture behavior.

Example 2.

5 Plates sized as in example 1 were manufactured by compression molding from a mixture of poly (L,D-lactide) (85/15 L/D ratio) and hydroxyapatite with particle size of 60 μm reinforced unidirectionally with poly (L-lactide) fibers. Poly (L,D-lactide) and hydroxyapatite were previously melt mixed to a film form. The composition had 48/21/31 weight percent of matrix polymerhydroxyapatite-polymer
10 fibers, respectively. Three-point bending strength (yield) and modulus were 116.6 MPa and 6.1 GPa, respectively, and no sample fracture was detected.

Example 3.

 Plates sized approximately 50 x 10 x 1 mm were manufactured by
15 compression molding from the unidirectional prepreg material of poly (L,D lactide) (85/15 L/D ratio), hydroxyapatite and poly (L-lactide) fibers. The proportions of components varied from 3-16 wt-%, 15-50 wt-% and 48-85 wt-%, respectively. Three-point bending strength (yield) and modulus depended on the concentrations of the composite. Typical mechanical properties are listed in Table 3. No sample
20 fracture was detected and the behavior was ductile.

Table 3

PLDLA (85/15) matrix (wt-%)	PLLA fibers (wt-%)	Hydroxy apatite (wt-%)	Three-point bending strength (MPa)	Three-point bending modulus (GPa)
3	82	15	136	9.5
4	71	25	143	9.1
5	47	48	141	12.2
8	61	31	139	10.5
9	54	37	118	8.3
16	48	36	166	9.6

Example 4.

Plates sized as in example 3 were manufactured by compression molding from a prepreg material of poly (L,D-lactide) (85/15 L/D ratio), hydroxyapatite and poly (L-lactide) fibers. The proportions of components were 4 wt-%, 15 wt-% and 81 wt-%, respectively. Three sample types were manufactured having different prepreg lay-ups of 0°/0°/0°/0°/0°, 0°/45°/0°/-45°/0° and 0°/0°/90°/0°/0°. Three-point bending strengths (yield) and moduli were 135.9 MPa and 9.5 GPa, 140.1 MPa and 10.1 GPa, and 131.0 MPa and 9.3 GPa, respectively, and no sample fracture was detected.

Example 5.

The surfaces of three different samples were studied by Fourier Transform

Infrared Spectroscopy. Samples were:

a) hydroxyapatite

b) hydroxyapatite-poly (D,L-lactide)-poly (L-lactide) composite

c) poly (D,L-lactide)-poly (L-lactide) composite.

The spectras from these samples are shown in figure 2. Matching peaks are detectable with samples b and c, which are poly lactide peaks. There also occur matching peaks from samples a and b which are characteristic of calcium phosphate compounds. The bioactivity of the composites claimed in this invention is the result of hydroxyapatite on the surface.

Example 6.

Plates sized as in example 3 were manufactured by compression molding from the unidirectional prepreg material of racemic poly (D,L-lactide), tricalcium phosphate with mean particle size of 70 μ m and poly glycolide fibers. The proportions of components varied from 5 wt-%, 20 wt-% and 75 wt-%, respectively. Three-point bending strength (yield) and modulus were 195 MPa and 14.2 GPa, and no sample fracture was detected.

Example 7.

Plates sized as in example 3 were manufactured by compression molding from the prepreg material made of racemic poly (D,L-lactide), hydroxyapatite powder with mean particle size of 100 μ m and the fabric made of poly (L-lactide) and poly (L,D lactide) (96/4) fibers. The proportions of components varied from 5 wt-%, 20 wt-% and 75 wt-%, respectively. Three-point bending strength (yield) and modulus were 150 MPa and 11.8 GPa, and no sample fracture was detected. Specimens showed similar mechanical properties in both the warp and the weft directions of the fabric.

Example 8.

Plates sized as in example 1 were manufactured by compression molding from a mixture of poly (ortho ester) and hydroxyapatite with mean particle size of 80 μm reinforced unidirectionally with poly (ortho ester) fibers. Poly (ortho ester) matrix and hydroxyapatite were previously melt mixed to a film form. The composition had 50/20/30 weight percent of matrix polymerhydroxyapatite-polymer fibers, respectively. Three-point bending strength (yield) and modulus were 105 MPa and 9.7 GPa, respectively, and no sample fracture was detected.

10 Example 9.

Plates sized as in example 3 were manufactured by compression molding from the unidirectional prepreg material of copolymer of poly (D,L lactide) and poly-e-caprolactone, tricalcium phosphate with mean particle size of 80 μm and poly-e-caprolactone fibers. The proportions of components varied from 16 wt-%, 30 wt-% and 54 wt-%, respectively. Three-point bending strength (yield) and modulus were 86 MPa and 3.4 GPa, and no sample fracture was detected. The strength and modulus values were lower than those for lactide based composites, but the extension to yield was much higher.

20

Example 10.

Plates sized as in example 1 were manufactured by compression molding from a mixture of a copolymer of poly (hydroxybutyrate)-poly (hydroxyvalerate) and a mixture of hydroxyapatite and tricalcium phosphate (50/50) with mean particle size

of 120 μm , reinforced unidirectionally with poly (hydroxybutyrate) fibers. The polymer matrix and ceramic mixture were previously melt mixed to a film form. The composition had 30/30/40 weight percent of matrix copolymer-ceramic mixture-polymer fibers, respectively. Three-point bending strength (yield) and modulus were 122 MPa and 6.2 GPa, respectively, and no sample fracture was detected.

Example 11.

Two set of samples (plates with 5 mm width, 20 mm length and 0.9 mm thickness) were implanted to the back of rats (subcurris). Specimens were made of poly-L lactic acid fibers, poly-D,L-lactic acid matrix (with L/D ratio 85/15) and hydroxyapatite powder using prepreg manufacturing method. The quantities of the components were 80 wt-%, 5 wt-% and 15 wt-%, respectively. The plates had five prepreg layers, with layer alignments of $0^\circ/0^\circ/0^\circ/0^\circ/0^\circ$. The mean particle diameter of hydroxyapatite powder in the first set of plates was 7.43 micrometers and in the second set of plates was 80 ± 20 micrometers.. The plates were gamma sterilized with a dose of 2.5 MRads.

Five animals from both sets were sacrificed after one year of implantation. In histological studies it was clearly seen, that in and around the composite plates with finer hydroxyapatite powder there existed significantly more giant cells than in the tissue of reference animals containing composite plates with coarser hydroxyapatite particles. Thus, coarser hydroxyapatite particles were shown to be more biocompatible.

TABLE 1. Resorbable polymers suitable for biocomposites.

Polymer

Polyglycolide (PGA)

Copolymers of glycolide:

Glycolide/L-lactide copolymers (PGA/PLLA)

Glycolide/trimethylene carbonate copolymers (PGA/TMC)

Polylactides (PLA)

Stereocopolymers of PLA:

Poly-L-lactide (PLLA)

Poly-DL-lactide (PDLLA)

L-lactide/DL-lactide copolymers

Copolymers of PLA:

Lactide/tetramethylglycolide copolymers

Lactide/trimethylene carbonate copolymers

Lactide/d-valerolactone copolymers

Lactide/e-caprolactone copolymers

PLA/polyethylene oxide copolymers

Polydepsipeptides

Unsymmetrically 3,6-substituted poly-1,4-dioxane-2,5-diones

Poly-b-hydroxybutyrate (PHB)

PHB/b-hydroxyvalerate copolymers (PHB/PHV)

Poly-b-hydroxypropionate (PHPA)

Poly-p-dioxanone (PDS)

Poly-d-valerolactone
 Poly-ε-caprolactone
 Methylmethacrylate-N-vinyl pyrrolidone copolymers
 Polyesteramides
 Polyesters of oxalic acid
 Polydihydropyrans
 Polyalkyl-2-cyanocrylates
 Polyurethanes (PU)
 Polyvinylalcohol (PVA)
 Polypeptides
 Poly-β-malic acid (PM LA)
 Poly-β-alkanoic acids
 Polycarbonates
 Polyorthoesters
 Polyphosphates

Table 2. Bioceramics and glasses suitable for biocomposites.

Hydroxyapatite
 Tricalcium phosphate
 Other calcium phosphates
 Bioglass®
 Ceravital®
 Alumina

What is claimed is:

1 1. A biodegradable and bioactive composite material for surgical
2 osteosynthesis applications comprising: at least one resorbable polymeric matrix
3 component, at least one resorbable polymeric reinforcing element, and at least one
4 ceramic reinforcing element.

1 2. A method of manufacturing a biodegradable composite according to
2 claim 1, comprising the steps of:

3 a) selecting at least one first polymer for the matrix;

4 b) selecting at least one bioceramic for use as the ceramic reinforcing
5 element;

6 c) mixing said first polymer and said bioceramic together to form a
7 mixture;

8 d) selecting at least one second polymer in a fiber form;

9 e) placing said second polymer into a desired formation;

10 f) combining said mixture of step (c) and said formation of step (e) to
11 yield a second mixture; and

12 g) subjecting the second mixture of step (f) to heat or pressure.

ABSTRACT

Surgical osteosynthesis composite material which has three components: biodegradable polymer reinforcement, bioceramic or bioglass filler reinforcement and biodegradable polymer matrix. This invention relates to biodegradable materials used for bone fracture fixation devices and methods of their manufacture. Unlike other
5 known materials used prior to this application, the composites of this invention have two different reinforcing phases and one matrix phase. One reinforcing element is referred as the polymeric reinforcing element and the other as the ceramic reinforcing element.

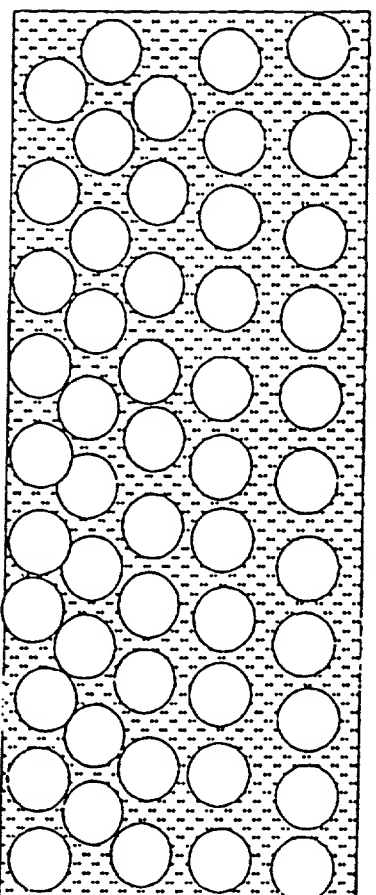
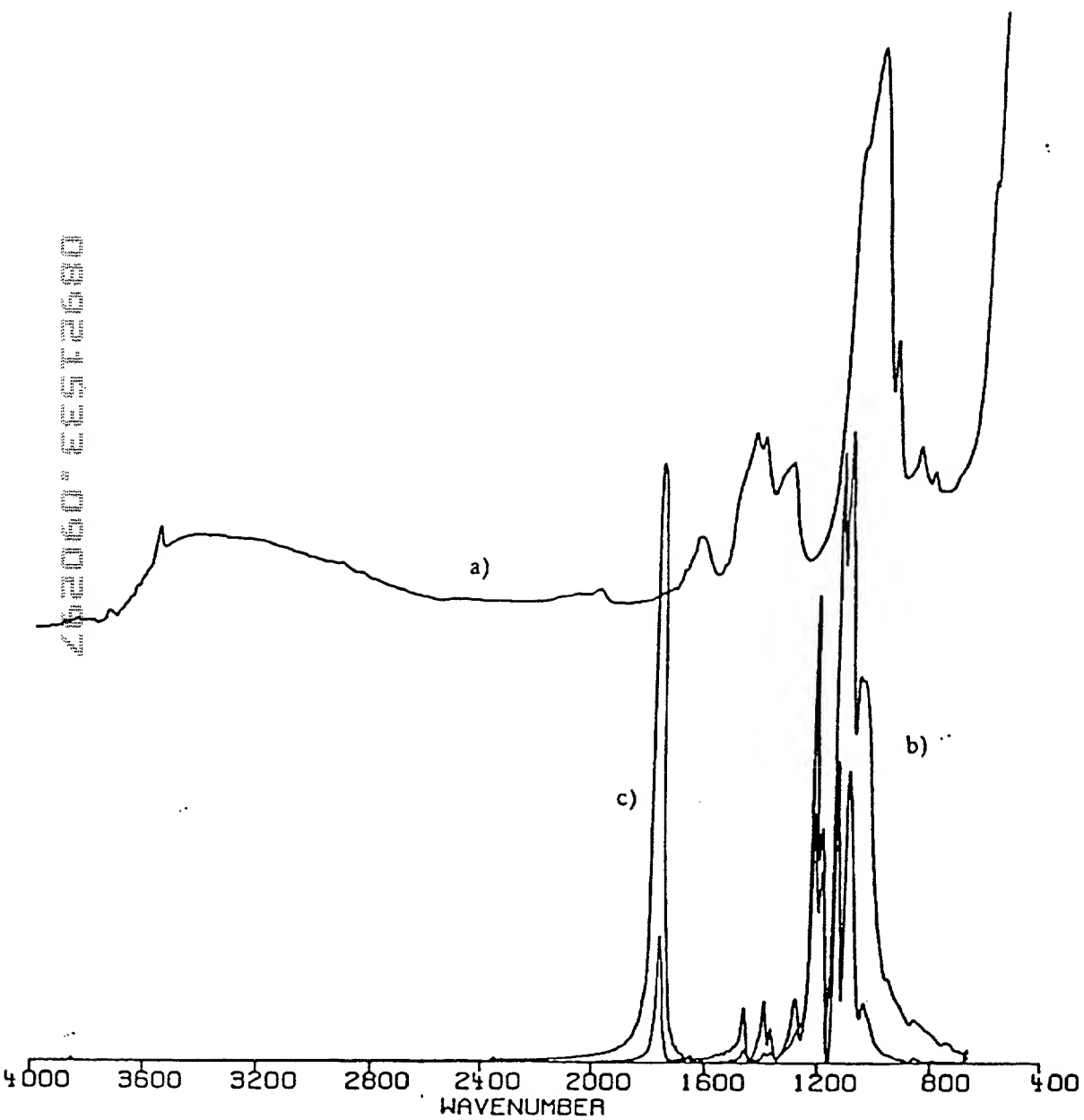


Figure 1.

○ Fibrillated polymer reinforcement

▤ Mixture of matrix polymer and bioceramic or glass

Figure 2.



DECLARATION AND POWER OF ATTORNEY

As a below named inventors, we hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled "**BIOACTIVE AND BIODEGRADABLE COMPOSITES OF POLYMERS AND CERAMICS OR GLASSES AND METHOD TO MANUFACTURE SUCH COMPOSITES**", the specification of which is filed in the U.S. Patent and Trademark Office herewith.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

We hereby claim the benefit under Title 35, United States Code, § 120, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

We hereby appoint Richard L. Mayer (Registration No. 22,490), Michael D. Loughnane (Registration No. 30,720), and Paul M. Richter, Jr. (Registration No. 36,254) my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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